Misunderstood MTBE

Your recent article panning methyl-*tert*-butyl ether use (*EHP* 102:913) was extremely misleading and focused on unpublished, and therefore not critically reviewed data, which is inconsistent with standards of scientific journals. Given the confusion caused by the article, you should provide more accurate information to your readers on why methyl-*tert*-butyl ether (MTBE) is in gasoline and how it is being managed in a manner protective of public health.

In 1990, Congress passed the Clean Air Act Amendments, which contained a requirement to include oxygen in fuel to reduce carbon monoxide (CO) emissions from motor vehicles. Once oxygenates were required by law, the industry began the process of tooling up for the production of oxygenated fuels. Either alcohols or ethers can be added to provide oxygen and both have been used previously. During the 1979 fuel crisis, alcohols had been added to gasoline to form gasohol. MTBE was added to gasoline as an octane enhancer after the lead phase-out. MTBE had also been used in a three-year pilot CO reduction program in the Southwest beginning in the winter of 1989–1990.

There was a considerable body of toxicological data on MTBE, including neurotoxicity studies, genetic toxicity studies, and reproduction and developmental studies. In addition, preliminary results were available from chronic bioassays in rats and mice prior to the onset of the winter fuels program. These results did not suggest MTBE would be hazardous, particularly at the low concentrations likely to be encountered in fuel use. Thus, required by law to add an oxygenate, industry legitimately made MTBE its principal choice. Ethanol, however, is also widely used, and other compounds such as ethyl-*tert*-butyl ether, *tert*-amyl methyl ether, and *tert*-butyl alcohol are being considered. Oxygenates have been added to winter fuel in 39 cities since November 1992 for CO reduction and are now in reformulated gasoline, which has been required to be sold in approximately 35 geographic areas to reduce ozone since January 1, 1995.

How has the oxygenate program fared? From the standpoint of CO reduction, it has been successful. EPA estimates that "a reduction of over 2 billion pounds of carbon monoxide annually is associated with the winter program." There have been a few complaints from users about reactions to the new product, something not surprising given MTBE's very distinctive ether odor. In 1989, there were a few complaints in the Southwest, but they disappeared in 1990 and 1991. With the initiation of the winter fuel program in 1992, there were scattered complaints in New York, Montana, and more frequent complaints in Alaska and New Jersey. Industry responded by collaborating with EPA to conduct several studies to assess exposure during normal activities and attempting to duplicate exposures to assess health effects in human volunteers in controlled laboratory situations.

The results of these studies were reassuring. Exposures during refueling and commuting were consistently low, averaging 0.3–0.5 ppm during refueling. Acute symptoms described in the complaints could not be replicated in clinical chamber studies (*1*). Finally, in a study comparing healthy garage workers exposed to high and low MTBE concentrations, no differences in self-reported symptoms could be demonstrated that were attributable to MTBE exposure (*2*).

We still hear reference to complaints in New Jersey, although principally from representatives of groups, not from individuals. We find these complaints perplexing since New Jersey law minimizes exposures by requiring stage II vapor recovery systems throughout the state and by not allowing self-service fueling stations. It is also interesting to note that oxygenated fuels are widely used in various parts of the United States, yet the complaints appear to be focused in New Jersey.

In summary, the government mandated the use of oxygenates in fuels, and the industry is complying with that mandate. There is a large body of toxicologic data about MTBE, which makes up the largest fraction of oxygenates currently in use. That data do not suggest untoward health effects from the very limited exposures encountered during normal use of gasoline. Both government and industry have managed introduction of MTBE and responded to legitimate complaints in an appropriate manner. The article you published was incorrect and misleading and not representative of the quality of articles that should appear in your publication.

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References

1. Prah JD, Goldstein GM, Devlin R, Otto D, Ashley D, House D, Cohen KL, Gerrity T. Sensory, symptomatic, inflammatory, and ocular responses to and the metabolism of methyl tertiary butyl ether in a controlled human exposure experiment. Inhal Toxicol 6:521–528 (1994).
2. Mohr SN, Fiedler N, Weisel C, Kelly-McNeil K. Health effects of MTBE among New Jersey garage workers. Inhal Toxicol 6:553–562 (1994).

Clarification

The November 1994 issue of *EHP* contained a forum article on methyl-*tert*-butyl ether that referred to the North Carolina scientific Advistory Board's review of the carcinogenicity data for MTBE. The conclusion of the article stated that "The Board concluded that the state should consider requesting that the EPA remove MTBE from gasoline because of the uncertainties surrounding it." This statement is incorrect. We did not make such a recommnedation. The following summary represents our report to the North Carolina Department of Environment, Health and Natural Resources.

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Summary of the Carcinogenicity Assessment of MTBE conducted by the Secretary's Scientific Advisory Board on Toxic Air Pollutants

Abstract. The Secretary's Scientific Advisory Board on Toxic Air Pollutants (SAB) examined the scientific evidence pertaining to MTBE carcinogenicity and came to a consensus agreement that, according to the National Toxicology Program (NTP) classification of carcinogenic activity, there is "some evidence" for carcinogenicity of MTBE in animals. The SAB agreed "some evidence" approximately corresponds to the "C" classification by the EPA. In an exception to the SAB policy of not quantifying risk for group C carcinogens, a range of exposures that could be associated with a potential

risk of 1 in 100,000 (1×10^{-5}) was calculated. This range is 0.04 mg/m^3 to 0.64 mg/m^3. The annual concentration estimated by the EPA that maximally exposed people would be subjected to in areas with a 4-month oxyfuel season ranges between 0.03 and 0.05 mg/m^3. SAB and EPA estimations indicate that the range of potential risk of maximally exposed people in North Carolina may be between 1×10^{-5} and zero at current exposure levels.

Data assessment. The merits and deficiencies of the scientific information relevant to MTBE carcinogenicity were considered carefully and are summarized below.

Two chronic inhalation studies have been performed, one on F344 rats, the other on CD-1 mice; exposures were 400, 3,000, and 8,000 ppm MTBE, 6 hours per day, 5 days per week (*1,2*). Problems with the studies include MTBE-induced toxicity (other than induction of neoplasms), decreased survival of high-dose animals, and substantially shorter than lifetime exposures. These problems impart considerable uncertainity to application of the resulting data to carcinogenicity hazard characterization.

An increase in kidney tumor incidence (combined adenomas and carcinomas) in male rats exposed to 3,000 ppm MTBE via inhalation was considered to contribute to the weight of evidence of carcinogenicity. There was no significant increase in tumor formation in male rats exposed to 8,000 ppm MTBE in the same study. The dose–response effect required to attribute the tumors to MTBE exposure unequivocally may not have been detected because the 8,000 ppm dose group was sacrificed 15 weeks before the 3,000 ppm group due to excess mortality among subjects. Had the high dose group lived longer, they may have developed tumors. The SAB considered the possibility that tumor formation was due to induction of α-2_u-globulin, a protein specific to male rats and not relevant to other animals or humans. The kidney tumors could not be attributed solely to induction of the α-2_u protein mechanism because an overabundance of α-2_u was not detected in histological sections of treated rats, though a pattern of pathology similar to that associated with α-2_u was observed. The SAB considered the possibility that kidney tumors observed in this study were secondary to toxicological damage resulting from exceedance of the maximum tolerated dose. Though kidney damage preceded tumors, a chronic study conducted by the NTP on a major metabolite of MTBE, *tert*-butyl alcohol (TBA), produced evidence of kidney tumors at a dose not exceeding the maximum tolerated dose when TBA was administered in drinking water. The male rat kidney tumors may not be attributed fully to the toxic effect of MTBE on the kidney, or to induction of α-2_u globulin, but may be due to a TBA-mediated mechanism. There are no data available to use for a quantitative comparison of rodent and human MTBE metabolism.

Increased interstitial cell adenoma tumor incidence observed in the testes of male rats in the inhalation study mentioned above was considered to contribute to the weight of evidence of carcinogenicity. A significant dose response in tumor incidence was seen from 64% in concurrent controls to 94% among the high-dose rats. The historical incidence of testicular adenomas in these rats ranges from 86 to 91%, but concurrent controls are generally considered the most appropriate controls for comparison. The high spontaneous background rate of testicular tumors in this strain of rat makes interpretation of the significance of the data difficult, but the clear dose–response effect compels the SAB to include these benign tumors in the weight of evidence of carcinogenicity.

Female CD-1 mice exposed to 8,000 ppm MTBE exhibited a significant increase in liver adenoma tumor incidence, which was considered part of the weight of evidence for carcinogenicity. No increase in tumor incidence was observed at the lower two doses. Body weight gain in mice exposed to 8,000 ppm was decreased 24% compared to controls, which may indicate the maximum tolerated dose was exceeded.

Male mice exposed to 8,000 ppm MTBE exhibited an increase in liver carcinoma incidence, which was considered part of the weight of evidence for carcinogenicity. Body weight gain in male mice exposed to 8,000 ppm was reduced by 15%, and the mortality rate of males was increased at this dose. These factors indicate the 8,000 ppm exposure may have exceeded the maximum tolerated dose in male mice.

A chronic study in which MTBE was administered to Sprague-Dawley rats by gavage in an olive oil vehicle reportedly has been conducted in Italy by Maltoni. A representative of Maltoni's laboratory, Dr. Myton Mehlman, reported "dose-related" increases in combined lymphoma and leukemias, hematoreticular tumors, uterine sarcomas, and testicular Leydig cell tumors in MTBE-treated rats. The experimental design and results of this study have not been sufficiently reported or reviewed to allow the information to be used in a weight-of-the-evidence evaluation of carcinogenicity.

The SAB concludes there is "some evidence" for carcinogenicity of MTBE in animals according to NTP guidelines for peer-reviewed data characterizing carcinogenic activity of chemicals. The board recognizes "some evidence" in the NTP classification system approximately corresponds to a "C" carcinogen in the EPA classification system. The board's policy as recommended in 1986 by the North Carolina Academy of Sciences is not to assess carcinogenicity risks for compounds the EPA has designated group C carcinogens. The SAB was asked specifically to review carcinogenicity of MTBE because its use as an oxygenate in gasoline could result in exposure of a large number of people to MTBE. In an exception to the policy of not quantifying risk for group C carcinogens, the board estimated a range of exposure levels that could be as high as 10^{-5} risk.

Assuming MTBE is a carcinogen in humans, the data from animal studies were used by the SAB to calculate an estimate of human risk due to exposure. The calculations were based on the kidney tumor incidence in male rats chronically exposed to 3,000 ppm of MTBE. Human unit risks were calculated using four different equations to estimate a range of ambient concentrations of MTBE which would pose an acceptable risk to a person exposed continuously for 70 years. An acceptable risk level of 10^{-5} was used, as suggested in the North Carolina Academy of Sciences Report and Recommendations to the Air Toxics Panel (*3*), for animal carcinogens (known human carcinogens are set at 10^{-6} risk). The range of concentrations at a risk of 10^{-5} calculated by the SAB was 0.04 mg/m^3 to 0.64 mg/m^3. A concentration range rather than a single concentration is submitted by the board to the Department of Environment, Health and Natural Resources because uncertainty inherent in the data makes one estimation no more realistic than another. The lower concentration is clearly the most conservative.

The EPA summary of health effects of MTBE contains exposure estimates for the general public based on limited sampling conducted at gas stations, at the property lines of gas stations, and inside commuting cars (*4*). These concentrations are purported to be reasonable worst-case estimates applicable to working adults who live near gas stations or major roadways. The annual MTBE concentration estimated by the EPA for maximally exposed people in areas with a four-month oxyfuel season ranges between 0.03 and 0.05 mg/m^3.

Conclusion. The SAB determined there is some evidence for carcinogenicity of MTBE in animals. The SAB estimated a human risk of cancer due to MTBE exposure by extrapolating from the animal data to estimate a risk to humans. The risk calculations were used to estimate concentrations of MTBE which would pose minimal risk to humans exposed continuously for 70 years. The range of concentrations calculated by the SAB expected to pose a 10^{-5} risk was 0.04 mg/m^3 to 0.64 mg/m^3. The EPA estimated that an adult commuter who lives next to a gas station could be exposed to 0.03 to 0.05 mg/m^3 of MTBE annually in a locale which has a four-month oxyfuel season. The SAB and EPA estimations indicate that the range of potential risk of maximally exposed people in North Carolina may be betweeen 1×10^{-5} and zero at current exposure levels.

References

1. Chun et al. Bushy Run Research Center. Docket no. OPTS 42908, 1992.
2. Burleigh-Flayer et al. Bushy Run Center. Docket no. OPTS 42908, 1992.
3. NCAS. Report and recommendations to the Air Toxics Panel. Raleigh, NC:North Carolina Academy of Sciences, 1986.
4. U.S. EPA. Assessment of potential health risks of gasoline oxygenated with MTBE. EPA 600/R-93/206. Washington, DC: U.S. Environmental Protection Agency, 1994.